

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository:<https://orca.cardiff.ac.uk/id/eprint/184561/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Kraft, Julia, Braun, Alice, Awasthi, Swapnil, Panagiotaropoulou, Georgia, Schipper, Marijn, Bell, Nathaniel, Posthuma, Danielle, Pardiñas, Antonio F. , Ripke, Stephan, Heilbron, Karl and Schizophrenia Working Group of the Psychiatric Genomics Consorti 2026. Identifying drug targets for schizophrenia through gene prioritization. *Translational Psychiatry* 10.1038/s41398-026-03813-0

Publishers page: <https://doi.org/10.1038/s41398-026-03813-0>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Identifying drug targets for schizophrenia through gene prioritization

Received: 1 February 2025

Revised: 5 December 2025

Accepted: 20 January 2026

Cite this article as: Kraft, J., Braun, A., Awasthi, S. *et al.* Identifying drug targets for schizophrenia through gene prioritization. *Transl Psychiatry* (2026). <https://doi.org/10.1038/s41398-026-03813-0>

Julia Kraft, Alice Braun, Swapnil Awasthi, Georgia Panagiotaropoulou, Marijn Schipper, Nathaniel Bell, Danielle Posthuma, Antonio F. Pardiñas, Stephan Ripke, Karl Heilbron & on behalf of the Schizophrenia Working Group of the Psychiatric Genomics Consortium

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

Identifying drug targets for schizophrenia through gene prioritization

Authors

Julia Kraft^{1,2,3,‡}, Alice Braun^{1,2,3,‡}, Swapnil Awasthi^{1,2,3}, Georgia Panagiotaropoulou^{1,2,3}, Marijn Schipper⁴, Nathaniel Bell⁴, Danielle Posthuma^{4,5}, Antonio F. Pardiñas⁶, Stephan Ripke^{1,2,3,†}, Karl Heilbron^{1,2,3,7,†,§} on behalf of the Schizophrenia Working Group of the Psychiatric Genomics Consortium*

Author affiliations

¹Department of Psychiatry and Psychotherapy, Charité – Universitätsmedizin Berlin, Berlin, Germany

²Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA

³German Center for Mental Health (DZPG), partner site Berlin/Potsdam, Berlin, Germany

⁴Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

⁵Department of Child and Adolescent Psychiatry and Pediatric Psychology, Section Complex Trait Genetics, Amsterdam Neuroscience, Vrije Universiteit Medical Center, Amsterdam, The Netherlands

⁶Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, UK

⁷Current address: Bayer AG, Research & Development, Pharmaceuticals, Berlin, Germany

[#]Equal contribution

[†]Equal contribution

[§]Corresponding author: kheilbro@broadinstitute.org

*A list of authors and their affiliations appears at the end of the paper.

ARTICLE IN PRESS

Abstract

Schizophrenia genome-wide association studies (GWASes) have identified >250 significant loci and prioritized >100 disease-related genes. However, gene prioritization efforts have mostly been restricted to locus-based methods that ignore information from the rest of the genome. To more accurately characterize genes involved in schizophrenia etiology, we applied a combination of highly-predictive tools to a published GWAS of 67,390 schizophrenia cases and 94,015 controls. We combined both locus-based methods (fine-mapped coding variants, distance to GWAS signals) and genome-wide methods (PoPS, MAGMA, ultra-rare coding variant burden tests). We extracted genes that 1) are targeted by existing drugs that could potentially be repurposed for schizophrenia, 2) are predicted to be druggable, or 3) may be testable in rodent models. We prioritized 101 schizophrenia genes, including 15 that are targeted by approved or investigational drugs (e.g., *DRD2*, *GRIN2A*, *CACNA1C*, *GABBR2*). Of these, 7 have never been tested in clinical trials for schizophrenia or other psychiatric disorders (e.g., *AKT3*). Seven genes are not targeted by any existing small molecule drugs, but are predicted to be druggable (e.g., *GRM1*). We prioritized two potentially druggable genes in loci that are shared with an addiction GWAS (*PDE4B* and *VRK2*). We curated a high-quality list of 101 genes that likely play a role in the development of schizophrenia. Developing or repurposing drugs that target these genes may lead to a new generation of schizophrenia therapies. Rodent models of addiction more closely resemble the human disorder than rodent models of schizophrenia. As such, genes prioritized for both disorders could be explored in rodent addiction models, potentially facilitating drug development.

Introduction

Schizophrenia is a highly-heritable and heterogeneous disorder characterized by positive symptoms (e.g. delusions and hallucinations), negative symptoms (e.g. blunted affect), and

cognitive impairment¹. Schizophrenia patients are often also diagnosed with neurodevelopmental disorders^{1,2} (e.g. intellectual disability and autism spectrum disorder) and other psychiatric conditions^{3,4} (e.g. substance use disorder [SUD] and depression). Antipsychotic medications antagonizing the dopamine receptor D2 are currently the first-line treatment for schizophrenia. However, approximately 34% of patients are considered treatment-resistant⁵, and especially cognitive deficits and negative symptoms often persist^{6,7}. These unmet clinical needs, as well as the high burden of antipsychotic side effects^{8,9}, clearly underline the necessity for pharmacotherapies with novel mechanisms of action.

Only 6.2% of psychiatric drug programs that enter Phase I trials are ultimately approved—well below the average success rate of 9.6% across all medical areas¹⁰—and investment in psychiatric drug development programs have decreased in recent years¹¹. This low success rate likely reflects the complex nature of mental disorders, limited knowledge of disease mechanisms, and sparsity of validated animal models. Given that 63% of drugs approved by the FDA from 2013–2022 were supported by human genetic evidence¹², pursuing targets that are genetically-linked to disease may lead to increased success rates^{13,14}. A major source of this human genetic evidence comes from genome-wide association studies (GWASes)^{13,14}. For instance, schizophrenia GWASes^{15–17} have identified a robust association near *DRD2*, which encodes the dopamine receptor D2. It is estimated that only 1.9% of genetically-supported drug targets for psychiatric disorders have been clinically explored¹⁸, suggesting that follow up of other schizophrenia GWAS findings may eventually lead to the design of new medicines.

Several studies have attempted to prioritize the causal genes underlying published schizophrenia GWAS loci using a variety of methods, including: expression quantitative trait loci mapping and transcriptome-wide association studies^{19–21}, massively parallel reporter assays²², summary data-

based Mendelian randomization (SMR)^{17,23}, and Hi-C-coupled MAGMA²⁴. The largest published schizophrenia GWAS identified 287 significant loci and prioritized 120 genes for follow up using fine-mapped credible sets²⁵, SMR²⁶, and Hi-C interactions between enhancers and promoters²⁷. However, a recent study has found that these methods vary substantially in their precision to correctly predict “probable causal genes” (defined using fine-mapped coding variants)²⁸. They found that only 29% of genes with the lowest SMR P-value in their locus were probable causal genes, while this proportion was even lower (~14%) for genes with the strongest promoter capture Hi-C evidence.

Here, we prioritized genes likely to play an important role in schizophrenia (SCZ) risk using high-precision prioritization methods: 1) polygenic priority score (PoPS) combined with nearest gene, 2) fine-mapped coding variants, and 3) and ultra-rare coding variant burden tests³⁰. We nominated 101 genes, 15 of which are targets of approved drugs (10 genes) or drugs that have been tested in clinical trials (“investigational drugs”, 5 genes). We discuss the potential utility of these drugs for treating schizophrenia and highlight an additional 7 prioritized genes that may be tractable via small molecule drugs.

Methods and Materials

Ethics statement

This research was conducted in accordance with the ethical standards of the institutional and national research committees. Informed consent was obtained from all participants. Details on Institutional Review Board approvals of the individual studies included in the presented work are provided in the original publication¹⁷.

GWAS summary statistics

We analyzed the publicly-available “core dataset” of GWAS summary statistics from the largest published SCZ GWAS from the Psychiatric Genomics Consortium (hereafter we will refer to this study as “PGC3”)¹⁷, a meta-analysis of 90 cohorts of European (EUR) and East Asian (EAS) descent including 67,390 cases and 94,015 controls (effective sample size [N_{eff}] = up to 156,797). For analyses requiring data from a single ancestry, we used the EUR subset of the core dataset (76 cohorts, 53,386 cases, 77,258 controls, effective sample size [N_{eff}] = up to 126,282) and the EAS-ancestry subset (14 cohorts, 14,004 cases, 16,757 controls, N_{eff} = up to 30,515).

Reference panels

Accordingly, we used external data from the Haplotype Reference Consortium release 1.1 (HRC) to construct three linkage disequilibrium (LD) reference panels: an EUR panel ($N \geq 16,860$), an EAS panel ($N \geq 538$), and an EUR+EAS panel that included both EUR and EAS individuals in the same proportions as the GWAS summary statistics—80% EUR and 20% EAS ($N_{\text{EUR}} = 2,191$, $N_{\text{EAS}} = 538$).

Variant quality control

We removed EUR+EAS GWAS variants with: 1) a minor allele count < 10 (minor allele frequency [MAF] < 0.0018) in the EUR+EAS reference panel (259 variants removed), 2) a reported allele frequency that differed from the reference panel frequency by > 0.1 (29 variants removed), and 3) a reported allele frequency that differed from the reference panel frequency by > 12-fold (11 variants removed). After quality control, 7,584,817 variants remained.

Isolating independent association signals

In order to disentangle statistically-independent genetic signals in the EUR+EAS dataset, we first clumped variants using PLINK v1.9³¹ ($P < 5 \times 10^{-8}$, $r^2 < 0.1$, window size = 3Mbp) and our EUR+EAS reference panel, expanded the boundaries of each clump by 500kb on either side, and merged overlapping boundaries. Within each resulting region, we ran COJO³² and removed hits with joint $P > 5 \times 10^{-8}$. If multiple independent hits in a region were found, we used COJO to isolate each signal by performing leave-one-hit-out conditional analysis. For each isolated signal, we computed credible sets (CSs) using the finemap.abf function in the coloc R package^{33,34}. Finally, we defined loci as ± 300 kb around each credible set.

MAGMA

We performed gene-based association tests using MAGMA²⁹ (“SNP-wise mean model”) and all variants with MAF > 1%. We analyzed the EUR- and EAS-based GWASes separately using the corresponding ancestry-specific reference panel and MAFs. We mapped variants to protein-coding genes using Genome Reference Consortium Human Build 37 (GRCh37) gene start and end positions from GENCODE v44³⁵. We removed genes that had fewer than 3 variants mapped to them. For each gene, we meta-analyzed the resulting ancestry-specific MAGMA z-scores weighted by the square root of sample size³⁶.

PoPS

MAGMA z-scores can be thought of as a proxy for the magnitude of effect that each gene has on schizophrenia risk. As such, PoPS²⁸ seeks to learn the properties of schizophrenia risk genes by training a ridge regression model to predict MAGMA z-scores using more than 57,000 gene-level features. These include 40,546 features derived from bulk and single-cell gene expression datasets (e.g., principal components of expression and cell type-specific expression), 8,718 features derived from predicted protein-protein interaction networks from InWeb_IM, and 8,479

features derived from curated biological pathways (e.g., the gene ontology and Reactome databases^{37,38}). PoPS output values are the fitted values of this ridge regression model, and represent the MAGMA z-score that a gene is predicted to have based on its properties. The original PoPS study recommended selecting the gene with the largest PoPS value in the locus rather than using a specific numerical threshold²⁸. Using the ancestry-specific MAGMA results as input, we performed PoPS²⁸ using all 57,543 gene-based features as predictors. These features were not available for chrX so we restricted our analysis to autosomal genes. The resulting ancestry-specific PoPS values were then also meta-analyzed weighted by the square root of sample size. We only used the meta-analyzed MAGMA and PoPS values for gene prioritization.

This same study introduced a novel tool for gene prioritization, the polygenic priority score (PoPS). By intersecting genes with the top PoPS value in their locus with genes that were nearest to their GWAS signal, they were able to achieve a precision of 79%.

Gene prioritization criteria

Following the original PoPS publication, we prioritized genes that met both of the following criteria: 1) had the top PoPS value in a given locus and 2) were the nearest gene to the corresponding GWAS signal based on the posterior inclusion probability (PIP)-weighted average position of credible set variants. Under these criteria, however, it is possible that the top PoPS value within a locus is relatively weak on a genome-wide scale, or that the nearest gene is nevertheless relatively distant. We therefore also required that genes have a PoPS value in the top 10% of all values genome-wide. We also prioritized genes that had 1) PIP > 50% for non-synonymous credible set variants affecting the gene, or 2) false discovery rate-corrected P value (P_{FDR}) < 5% in a published SCZ burden test of ultra-rare coding variants³⁰. We used non-synonymous variants from the “baseline-LF 2.2.UKB model” (80,693 variants) and subsetted to those with an estimated

per-variant heritability $> 1 \times 10^{-7}$ (removed 4,709 variants, all with estimated $h^2 < 1 \times 10^{-10}$: $> 1,000$ -fold smaller)³⁹. We removed loci that contained more than 20 genes since larger loci are more challenging to resolve⁴⁰, but we have included results for these large loci in Table S3.

Comparison with previous schizophrenia gene prioritization efforts

We compared our prioritized genes with those highlighted in the original PGC3 publication. Specifically, we extracted the “Symbol.ID” and “Prioritised” columns from Table S12. While the PGC3 study utilized the same core dataset, they restricted analysis to loci that retained genome-wide significance in the “extended GWAS”—a meta-analysis of the core dataset, 9 cohorts of African American and Latin American ancestry, and a dataset from deCODE genetics. They prioritized genes using a combination of FINEMAP, SMR, Hi-C interaction mapping, and non-synonymous or untranslated region credible set variants with PIP $> 10\%$. The PGC3 study validated their list of prioritized genes by looking for overlap with genes expressed in brain tissue, genes with signatures of mutation intolerance in large-scale exome studies⁴¹, or genes linked to schizophrenia through rare genetic variation in the SCHEMA study³⁰. Furthermore, they also found genetic overlaps in other neurodevelopmental conditions using sequencing studies from autism spectrum disorder⁴² and developmental disorder⁴³. We incorporated a subset of this information by extracting the “ASD” and “DDD” columns from Table S12 of the PGC3 study. For full details, please refer to the original publication¹⁷.

PsyOPS

We further validated our prioritized genes using the Psychiatric Omnilocus Prioritization Score (PsyOPS) tool⁴⁴. The original PsyOPS publication⁴⁴ found that PsyOPS achieved similar performance to PoPS in predicting causal psychiatric disease genes, but using only three predictors: probability of loss-of-function intolerance (pLI) > 0.99 , brain-specific gene expression,

and overlap with 1,370 known genes for neurodevelopmental disorders (autism, epilepsy, intellectual disability). PsyOPS treats the nearest gene to each GWAS hit as a proxy for the causal gene in the locus, trains leave-one-chromosome-out logistic regression models, and outputs the predicted probability that a given gene is causal. We determined a gene to be prioritized by PsyOPS if the predicted probability of being a causal gene exceeded 50%. We computed PsyOPS scores using all 257 independent schizophrenia GWAS hits.

Drug target mapping

We determined whether our prioritized genes were targeted by approved or investigational drugs using GraphQL API queries of the Open Targets platform⁴⁵, which in turn queries the EMBL-EBI ChEMBL database. For genes that were not targeted by approved or investigational drugs, we performed additional Open Targets API queries to extract evidence of drug tractability—the probability of identifying a drug that is able to bind and modulate a given target. We focussed on small molecule drugs, but results for other modalities can be found in Figure S1.

Colocalization with other studies

We prioritized several genes that have also been highlighted by recent GWASes for addiction⁴⁶ and Parkinson's disease⁴⁷. Using the EUR reference panel, we processed EUR-ancestry GWAS summary statistics from these studies using the same pipeline described above. We identified loci that physically overlapped with schizophrenia loci and computed the posterior probability of colocalization (H_4) using all variants in the shared locus and the coloc.abf function in the coloc R package^{33,34}.

Results

We prioritized schizophrenia genes using the “core dataset” from the largest published schizophrenia GWAS meta-analysis¹⁷, “PGC3” (67,390 cases and 94,015 controls). We identified

257 independent associations with $P < 5 \times 10^{-8}$ (Table S1). Across these loci, we prioritized 101 schizophrenia genes (Figure 1, Table S2) based on their distance to the credible set, PoPS values, number of genes in the locus, presence of non-synonymous variants in the credible set, and support from a published schizophrenia burden test of ultra-rare coding variants³⁰ (see Methods). To corroborate our findings with convergent evidence, we compared them with prioritization efforts from the PGC3 study¹⁷, genes linked to autism spectrum disorder⁴² (ASD) and developmental disorder⁴³ (DD) via sequencing studies, and results from the PsyOPS tool (Figure 2). Across all genes in GWAS loci, prioritized genes were also DD and/or ASD genes (Fisher's exact test $P = 7.8 \times 10^{-11}$, odds ratio [OR] = 11) or PsyOPS genes (Fisher's exact test $P = 1.7 \times 10^{-8}$, OR = 18) significantly more often than expected due to chance.

Overlap with previous schizophrenia gene prioritization efforts

Of our 101 prioritized genes, 37 (37%) were also prioritized in the PGC3 study ("overlapping genes") and several sources of evidence suggest that these genes are likely to play a role in schizophrenia risk. Ultra-rare coding variant burden in two overlapping genes (*GRIN2A* and *SP4*) was significantly associated ($P_{FDR} < 5\%$) with schizophrenia in the SCHEMA study³⁰. Similarly, five overlapping genes (*GRIN2A*, *CACNA1C*, *BCL11B*, *RERE*, and *SLC39A8*) were also identified by rare variant exome sequencing studies of DD⁴³ and/or ASD⁴² (see Figure 2). Furthermore, the lead schizophrenia variant in the *SLC39A8* locus is a non-synonymous variant (PIP = 99%) that has been investigated in detail elsewhere⁴⁸. *WSCD2* (PIP = 53%) and *THAP8* (PIP = 88%) were also prioritized due to a non-synonymous variant in the credible set. Four overlapping genes (*GRIN2A*, *DLGAP2*, *GABBR2*, and *CSMD1*) were nominated by PsyOPS (see Methods). Notably, *CSMD1* is known to inhibit the complement cascade, has reduced expression in first-episode psychosis patients⁴⁹, and knockout mice have exhibited behaviors resembling schizophrenia negative symptoms⁵⁰.

Genes that were not nominated by previous schizophrenia gene prioritization efforts

Of our 101 prioritized genes, 64 (63%) were not prioritized in the PGC3 study (“non-overlapping genes”). Two non-overlapping genes (*STAG1* and *FAM120A*) were significantly associated with ultra-rare coding variant burden in the SCHEMA study³⁰. Twelve non-overlapping genes (*STAG1*, *ZEB2*, *MYT1L*, *TBL1XR1*, *SATB2*, *MEF2C*, *CUL3*, *BCL11A*, *KMT2E*, *FOXP1*, *EP300*, and *TCF4*) were also identified by rare variant exome sequencing studies of DD⁴³ and/or ASD⁴². Note that *TCF4* was not prioritized in the PGC3 study because they only investigated regions containing three independent genetic associations or fewer and there were four associations near *TCF4*. We prioritized *PPP1R26* due to a non-synonymous variant in the credible set (PIP = 96%). Six non-overlapping genes (*ZEB2*, *MYT1L*, *SATB2*, *HCN1*, *RIMS1*, and *CACNA1I*) were nominated by PsyOPS (see Methods). Perhaps most importantly, our analysis highlighted the dopamine receptor gene *DRD2*, which is targeted by approved antipsychotic medications with varying affinity⁵¹ (Figure 3A). Finally, 31 of our 101 prioritized genes (31%) were not prioritized by PGC3, but have been highlighted by recent studies that prioritized schizophrenia genes using gene co-expression^{52,53}, expression quantitative trait loci mapping or TWAS^{20,54}, epigenome-wide association study⁵⁵, massively parallel reporter assays⁵⁶, or 3D genome architecture analysis⁵⁷ (e.g., *AP3B2*, *CACNB2*, *CNOT1*, *MEF2C*, *RBM26*, *SATB2*; see Supplemental Material; Table S2).

East Asian-specific gene prioritization

Because East Asian-ancestry individuals were underrepresented in our dataset relative to European-ancestry individuals, we tested whether applying our prioritization criteria to the East Asian cohort would identify additional ancestry-specific genes. There were eight genome-wide significant loci in the East Asian-only dataset. In these loci, we prioritized four genes: two that

were also found in the multi-ancestry meta-analysis (*VRK2* and *SPATS2L*) and two that were specific to the East Asian dataset (*FRY* and *PTN*). The *FRY* locus was not genome-wide significant in the multi-ancestry meta-analysis. Although the *PTN* locus was genome-wide significant in the multi-ancestry meta-analysis and *PTN* had the top local PoPS value, it was not the nearest gene and was therefore not prioritized.

Drug target mapping

In addition to *DRD2*, we prioritized 15 genes that are targeted by approved (10 genes) or investigational drugs (5 genes, Table S4, Table 1). Of these, 8 were also prioritized in the PGC3 study (*GRIN2A*, *CACNA1C*, *PDE4B*, *GABBR2*, *AKT3*, *DPYD*, *ACE*, and *ATP2A2*) and 7 (*CACNB2*, *GRM3*, *SNCA*, *CACNA1I*, *CD47*, *KCNJ3*, and *CHRNA3*) were prioritized in our analysis but not in PGC3 (see Discussion). Our list of prioritized genes also included 7 genes (*HCN1*, *VRK2*, *TRPC4*, *EP300*, *GRM1*, *PTPRF*, and *MMP16*) that belong to known druggable protein families⁵⁸ and are reported to bind to at least one high-quality ligand⁴⁵, suggesting potential as small molecule drug targets (Figure S1).

Discussion

We prioritized 101 genes near 257 independent GWAS signals. Of these genes, 52 (51%) were also supported by evidence (Figure 2) from the PGC3 study (37 genes), DD/ASD sequencing studies (17 genes), and PsyOPS (10 genes). We prioritized *DRD2* (Figure 3A)⁵¹, as well as 15 other genes targeted by approved drugs (10 genes) or drugs that have been tested in clinical trials (5 genes). Of these, only 8 genes were targeted by drugs that have been trialed in schizophrenia or other psychiatric disorders (see Table 1).

Some of these druggable genes have also been highlighted by earlier drug repurposing studies,

including genes that are targeted by drugs affecting calcium signaling (*CACNA1C*^{19,59–61}, *CACNA1I*^{60,61}, *CACNB2*^{59,60}), glutamatergic (*GRIN2A*^{19,59,60}, *GRM3*^{59,61}), GABAergic (*GABBR2*⁶⁰) and cholinergic pathways (*CHRNA3*⁶⁰). Our analyses do not predict whether the effect of these drugs (e.g. inhibitor) aligns with the effect that would be desired for schizophrenia. Therefore, we will now discuss literature supporting the potential for these drugs to be repurposed as treatments for schizophrenia. We also identified 7 other genes that may represent tractable small molecule drug targets and discuss how additional target validation could stimulate drug development programs.

Glutamate receptors: GRIN2A, GRM3, and GRM1

We prioritized *GRIN2A*, which encodes a subunit of the N-methyl-D-aspartate receptor (NMDA-R, Figure 3B). In addition to GWAS, there is evidence that decreased NMDA-R function increases schizophrenia risk from *GRIN2A* ultra-rare variant burden tests³⁰, *GRIN2A* mouse knockout models⁶², and pharmacological antagonism of the NMDA-R⁶³. This raises the possibility that increasing NMDA-R activity may provide therapeutic benefit for schizophrenia patients. A meta-analysis of 4,937 schizophrenia patients from 40 randomized controlled trials found that NMDA-R modulator augmentation (e.g. via glycine or glycine transporter type I inhibitors) significantly improved total, positive, and negative schizophrenia symptoms versus placebo⁶⁴. These compounds have also been proposed as a therapeutic strategy for schizophrenia patients who are treatment-resistant or have impaired cognition⁶⁵. There are currently three Phase III clinical trials underway assessing the effect of icloperkin, a glycine transporter type I inhibitor, on cognitive impairment associated with schizophrenia⁶⁶. If ultimately approved, this may become the first medication indicated to treat the cognitive symptoms of schizophrenia.

We also prioritized *GRM3*, which encodes a different glutamate receptor: metabotropic glutamate receptor 3 (mGluR₃). Clinical trials of pomaglumetad methionil, an mGluR_{2/3} agonist, have yielded inconclusive effects on positive symptoms^{67,68–71}. However, an analysis of clinical trial data suggested that specific patient subgroups may have benefited⁷² and preclinical research has suggested that a cognitive endpoint may be more appropriate^{73,74}. Similarly, positive modulation of mGluR₁ (encoded by *GRM1*) showed pro-cognitive effects in animal studies (e.g., reversal of working memory deficits) possibly via interneuronal regulation of cortical inhibition⁷⁵. mGluR1 activation also decreases striatal dopaminergic neurotransmission, which could lead to antipsychotic-like properties (e.g., reduction in positive symptoms)⁷⁶. Interestingly, the newly approved schizophrenia drug, KarXT, attenuates dopamine release and exerts antipsychotic-like effects by activating M4 muscarinic acetylcholine receptors^{77,78}. This process appears to be codependent on mGluR1 activation⁷⁷.

Voltage-gated calcium channels: CACNA1C, CACNB2, and CACNA1I

We prioritized CACNA1C (Figure 3C), which encodes the alpha-1 subunit of a voltage-gated calcium channel (Ca_v1.2). A Phase III clinical trial for bipolar disorder showed that 11 out of 13 non-responders to first-line therapy (lithium) showed a clinically-meaningful response to verapamil (a calcium channel blocker [CCB]), or verapamil + lithium⁷⁹. The genetic correlation between schizophrenia and bipolar disorder is approximately 70%² and a recent bipolar disorder GWAS also identified a significant association near CACNA1C⁸⁰, suggesting that verapamil may be a promising treatment option for schizophrenia. Other CCBs may also be effective—a large cohort study (N = 10,460) found that use of dihydropyridine CCBs was associated with reduced risk of psychiatric rehospitalization⁸¹. CCBs may also improve certain cognitive functions^{82,83}. The use of CCBs for treating schizophrenia is further supported by the fact that we prioritized CACN2B, an auxiliary subunit of voltage-gated calcium channels. A T-type calcium channel

antagonist targeting $\text{Ca}_{\text{v}}3.3$ (encoded by *CACNA1I*) has been tested in schizophrenia patients in a phase II trial, which produced inconclusive evidence since neither the investigated drug (MK-8998) nor the active comparator (olanzapine) showed significant symptom improvement⁸⁴.

Loci shared with addiction: PDE4B and VRK2

We prioritized *PDE4B*, which encodes phosphodiesterase 4B (Figure 3E). A recent GWAS of an addiction-related latent factor derived from four SUDs⁴⁶ also found a signal near *PDE4B* and highlighted *PDE4B* as the likely causal gene. SUDs are frequently comorbid with schizophrenia⁴ and there is significant genetic correlation between schizophrenia and several SUDs⁸⁵. While it is challenging to assess psychotic symptoms in rodents, high-quality rodent addiction models exist for a wide range of substances⁸⁶. Indeed, several drugs that are approved to treat alcohol use disorder (e.g. naltrexone and acamprosate) were originally pursued based in part on success in preclinical animal models^{86,87}. Administering ibudilast, a drug that inhibits *PDE4B* and other phosphodiesterases, has been shown to reduce alcohol intake by approximately 50% in rats⁸⁸ and decrease the odds of heavy drinking by 45% in a randomized clinical trial in humans⁸⁹. Given that both addiction and schizophrenia GWASes have suggested an important role for *PDE4B* in disease risk, *PDE4B* inhibitors may also benefit schizophrenia patients. A Phase I study in 15 schizophrenia patients found that roflumilast, an inhibitor of all four *PDE4* phosphodiesterases, significantly improved verbal memory, but not working memory⁹⁰.

We prioritized *VRK2*, which encodes vaccinia-related kinase 2 (Figure 3F). While the role of *VRK2* in schizophrenia remains unclear, it is expressed in microglial cells and a mechanism involving synaptic elimination by microglial cells has been proposed^{91,92}. Like *PDE4B*, the same addiction GWAS⁴⁶ also found an association near *VRK2*. The addiction and schizophrenia signals colocalize ($H_4 = 92\%$), suggesting a shared causal variant. Therefore, modulating *VRK2* activity

might result in clinical benefit for people with SUD and/or schizophrenia. VRK2 is a member of the highly-druggable serine/threonine kinases group of enzymes⁵⁸ and has been co-crystallised with a small molecule ligand⁹³. VRK2 modulation could be tested in rodent addiction models and, if successful, may warrant further testing in human clinical trials of SUD and SCZ patients.

Three other prioritized genes reside in loci shared with the addiction GWAS⁴⁶: *DRD2*, *SLC39A8* ($H_4 = 100\%$), and *PLCL2* ($H_4 = 74\%$). Although our analyses did not find evidence that *SLC39A8* and *PLCL2* are easily druggable by small molecule drugs, knockdown or overexpression of these genes in rodent addiction models may nevertheless improve our understanding of the shared biology of addiction and schizophrenia.

GABBR2

We prioritized *GABBR2*, which encodes the gamma-aminobutyric acid (GABA) type B receptor and is known to inhibit neuronal activity via downstream signaling cascades (Figure 3D). A Phase II clinical trial is currently testing whether arbaclofen, a GABA_B receptor agonist, can rescue ASD symptoms⁹⁴. Both post-mortem and *in vivo* studies identified reduced GABA levels in schizophrenia patients compared to controls, and impaired gamma band oscillations—which are linked with GABAergic signaling—are associated with schizophrenia^{95–99}. If proven to be a successful therapy for ASD, arbaclofen may therefore represent an interesting drug repurposing candidate for schizophrenia, particularly for symptoms and socio-cognitive deficits that are shared between the two disorders^{100,101}.

AKT3

We prioritized *AKT3*, the member of the AKT serine/threonine-protein kinase gene family with the highest brain-specific expression. Capivasertib—an inhibitor of all three AKT kinases—was

recently approved by the FDA to treat a subset of breast cancer patients¹⁰². However, AKT inhibition can lead to adverse psychiatric side effects¹⁰³ and *AKT3* knockout or knockdown resulted in cognitive deficits and reduced brain size in mice^{104,105}. Further studies are necessary to determine whether overall or isoform-specific⁵⁴ increases in AKT3 activity would benefit schizophrenia patients without increasing cancer risk.

SNCA

We prioritized *SNCA*, which encodes α -synuclein (α -syn). α -syn aggregates are the pathological hallmark of Parkinson's disease (PD) and antibodies targeting aggregated α -syn have been tested in two Phase II clinical trials for PD, although neither meet their primary endpoint^{106,107}. The schizophrenia association near *SNCA* colocalizes ($H_4 = 85\%$) with an association from a recent European-ancestry PD GWAS⁴⁷. The schizophrenia risk allele was associated with increased PD risk, which is in turn linked to increased α -syn production¹⁰⁸. As such, interventions that decrease α -syn production may benefit both PD and schizophrenia patients.

Besides *AKT3* and *SNCA*, there are 4 other genes that are targeted by approved or investigational drugs but have not been investigated in clinical trials of any psychiatric disorders. These include *CD47*, *KCNJ3*, *DPYD* and *ATP2A2*.

Limitations

The PGC3 study prioritized 83 genes that were not prioritized in our study. The majority of these (49 genes) were prioritized via SMR. We did not include SMR because it only demonstrated a precision of 29% when predicting a “gold standard” dataset of causal and non-causal trait-gene pairs²⁸, consistent with recent models for systematic differences between variants highlighted by GWAS and expression studies¹⁰⁹. The precision of SMR-nominated genes that failed to meet our

gene prioritization criteria is therefore likely to be lower than 29%. Only one additional gene (*CLCN3*) had SMR evidence and the top PoPS value in its locus. The PGC3 study prioritized an additional 26 genes where the entire credible set resided within the gene body, but did not have the top PoPS value. These included 6 non-coding genes: *AC068490.2*, *CTD-2008L17.2*, *LINC00320*, *LINC01088*, *RP11-399D6.2*, and *RP11-507B12.2*. The original PoPS study estimated that nearest genes without PoPS evidence had a <27% probability of being a “probable causal gene”²⁸. In the PoPS study, selecting the top-ranked gene in a locus led to a higher precision than including all genes above a specific threshold²⁸. While we nominated only one gene per locus, some loci may contain multiple causal genes.

The original PGC3 study performed gene prioritization analyses in the “core dataset”. This excluded individuals of African (AFR) or Latin American (LAT) ancestry found in the “extended dataset”. To ensure consistency with the original PGC3 study, we also analyzed the core dataset. Furthermore, the AFR and LAT datasets only included GWAS summary statistics, not individual-level genotypes, preventing us from identifying well-matched LD reference panels—something particularly important for admixed populations¹¹⁰. Nevertheless, we stress the importance of expanding gene prioritization to include more ancestries to ensure that findings are generalizable to a broader range of people.

Finally, we assembled our list of prioritized schizophrenia genes using *in silico* methods. Future functional validation studies are critical for dissecting the biological processes underpinning schizophrenia risk and for selecting candidate targets for drug development or repurposing.

Conclusion

We have curated a high-quality list of 101 genes that likely play a role in the development of schizophrenia. Developing or repurposing drugs that target these genes may lead to a new generation of schizophrenia therapies. Reassuringly, we prioritized several genes targeted by drugs that have been approved for schizophrenia (*DRD2*) or shown promising results in clinical trials (e.g., *GRIN2A*, *CACNA1C*, *CACN2B*). We prioritized genes that likely also play a role in SUD (e.g., *PDE4B*, *VRK2*). Drugs that modulate the activity of these genes could be tested in high-quality rodent models of addiction and, if shown to be safe and effective, should be considered for human clinical trials for SUD and/or schizophrenia. We also prioritized 7 genes that have not been targeted in clinical trials, but are predicted to be druggable via small molecule drugs. Additional efforts that improve our understanding of how these genes influence schizophrenia risk on a molecular level may stimulate the initiation of new drug programs. As new drug modalities continue to be invented and refined, more genes will become druggable. We hope that our list of prioritized genes will ultimately facilitate the development of new medicines for people living with schizophrenia.

Acknowledgements

We thank SURF (www.surf.nl) for the support in using the Snellius National Supercomputer.

JK and SR were supported by the German Center for Mental Health (DZPG). AB, JK, AFP, and SR were supported by the European Union's Horizon program (101057454, "PsychSTRATA"). AB and SR were supported by The German Research Foundation (402170461, grant "TRR265"). DP and MS were supported by The Netherlands Organization for Scientific Research (NWO Gravitation: BRAINSCAPES: A Roadmap from Neurogenetics to Neurobiology - Grant No. 024.004.012). DP was supported by The European Research Council (Advanced Grant No ERC-2018-AdG GWAS2FUNC 834057). AFP, NB, and DP were supported by the European Union's Horizon program (964874, "REALMENT"). AFP was supported by an Academy of Medical Sciences "Springboard" award (SBF005\1083). KH was supported by a Humboldt Research Fellowship from the Alexander von Humboldt Foundation. GP, SA, DP, SR, and the research reported in this publication were supported by the National Institute Of Mental Health of the National Institutes of Health under Award Number R01MH124873. The content is the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of Interest

JK, AB, SA, GP, MS, NB, DP, and SR have nothing to disclose. AFP reports receiving a grant from Akrivia Health for a project unrelated to this submission. KH is a former employee of 23andMe, Inc. and owns 23andMe, Inc. stock options.

Author Contributions

JK: software, methodology, validation, formal analysis, writing - original draft, visualization. AB: software, methodology, validation, formal analysis, writing - original draft, visualization. SA: validation, writing - review & editing. GP: validation, writing - review & editing. MS: validation, writing - review & editing. NB: validation, writing - review & editing. DP: supervision, resources, funding acquisition, writing - review & editing. AFP: validation, writing - review & editing. The Schizophrenia Working Group of the Psychiatric Genomics Consortium provided all schizophrenia genome-wide association study results. SR: conceptualization, validation, supervision, resources, funding acquisition, writing - review & editing. KH: conceptualization, methodology, software, validation, formal analysis, writing - original draft, visualization, supervision.

Schizophrenia Working Group of the Psychiatric Genomics Consortium

Julia Kraft^{1,2,3}, Alice Braun^{1,2,3}, Swapnil Awasthi^{1,2,3}, Georgia Panagiotaropoulou^{1,2,3}, Danielle Posthuma^{4,5}, Antonio F. Pardiñas⁶, Stephan Ripke^{1,2,3}

A full list of members appears in the Supplementary Information.

Data availability statement

ChEMBL Database: <https://www.ebi.ac.uk/chembl/>

HRC reference release 1.1: <https://ega-archive.org/datasets/EGAD00001002729>

Gencode release 44: https://www.gencodegenes.org/human/release_44.html

OpenTargets platform: <https://platform-docs.opentargets.org/>

The PGC3 GWAS core dataset is available through the PGC data access portal:

<https://pgc.unc.edu/for-researchers/data-access-committee/data-access-portal/>

Summary statistics of the PGC3 GWAS are freely available for download:

<https://pgc.unc.edu/for-researchers/download-results/>

Code availability statement

Custom code used in the presented study is stored at https://github.com/kheilbron/cojo_pipe and <https://github.com/kheilbron/brett>

Additional software and code:

COJO: <https://yanglab.westlake.edu.cn/software/gcta/#COJO>

coloc: <https://github.com/chr1swallace/coloc>

MAGMA: <https://cncri.nl/research/magma/>

PLINK 1.9: <https://www.cog-genomics.org/plink/>

PoPS: <https://github.com/FinucaneLab/pops>

PsyOPS: <https://github.com/Wainberg/PsyOPS>

References

- 1 Owen MJ, Sawa A, Mortensen PB. Schizophrenia. *Lancet* 2016; **388**: 86–97.
- 2 Cross-Disorder Group of the Psychiatric Genomics Consortium. Electronic address: plee0@mgh.harvard.edu, Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell* 2019; **179**: 1469–1482.e11.
- 3 Lu C, Jin D, Palmer N, Fox K, Kohane IS, Smoller JW *et al.* Large-scale real-world data analysis identifies comorbidity patterns in schizophrenia. *Transl Psychiatry* 2022; **12**: 154.
- 4 Hunt GE, Large MM, Cleary M, Lai HMX, Saunders JB. Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990–2017: Systematic review and meta-analysis. *Drug Alcohol Depend* 2018; **191**: 234–258.
- 5 Potkin SG, Kane JM, Correll CU, Lindenmayer J-P, Agid O, Marder SR *et al.* The neurobiology of treatment-resistant schizophrenia: paths to antipsychotic resistance and a roadmap for future research. *npj Schizophrenia* 2020; **6**: 1–10.
- 6 Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the 'right stuff'? *Schizophr Bull* 2000; **26**: 119–136.
- 7 Civeri G, Gesi C, Mencacci C. Pharmacological treatment of negative symptoms in schizophrenia: update and proposal of a clinical algorithm. *Neuropsychiatr Dis Treat* 2019; **15**: 1525–1535.
- 8 Chow RTS, Whiting D, Favril L, Ostinelli E, Cipriani A, Fazel S. An umbrella review of adverse effects associated with antipsychotic medications: the need for complementary study designs. *Neurosci Biobehav Rev* 2023; **155**. doi:10.1016/j.neubiorev.2023.105454.
- 9 Iversen TSJ, Steen NE, Dieset I, Hope S, Mørch R, Gardsjord ES *et al.* Side effect burden of antipsychotic drugs in real life - Impact of gender and polypharmacy. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; **82**. doi:10.1016/j.pnpbp.2017.11.004.
- 10 Mullard A. Parsing clinical success rates. *Nat Rev Drug Discov* 2016; **15**: 447–447.
- 11 Munro J, Dowden H. Trends in neuroscience dealmaking. *Biopharma Dealmakers* 2018. doi:10.1038/d43747-020-00598-z.
- 12 Rusina PV, Falaguera MJ, Romero JMR, McDonagh EM, Dunham I, Ochoa D. Genetic support for FDA-approved drugs over the past decade. *Nat Rev Drug Discov* 2023; **22**: 864.
- 13 King EA, Davis JW, Degner JF. Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval. *PLoS Genet* 2019; **15**. doi:10.1371/journal.pgen.1008489.
- 14 Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y *et al.* The support of human genetic evidence for approved drug indications. *Nat Genet* 2015; **47**: 856–860.

- 15 Schizophrenia Working Group of the Psychiatric Genomics Consortium, Ripke S, Neale BM, Corvin A, Walters JTR, Farh K-H *et al.* Biological Insights From 108 Schizophrenia-Associated Genetic Loci. *Nature* 2014; **511**: 421.
- 16 Pardiñas AF, Holmans P, Pocklington AJ, Escott-Price V, Ripke S, Carrera N *et al.* Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat Genet* 2018; **50**. doi:10.1038/s41588-018-0059-2.
- 17 Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdely TB *et al.* Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* 2022; **604**: 502–508.
- 18 Minikel EV, Painter JL, Dong CC, Nelson MR. Refining the impact of genetic evidence on clinical success. *medRxiv*. 2023; : 2023.06.23.23291765.
- 19 Reay WR, Geaghan MP, Atkins JR, Carr VJ, Green MJ, Cairns MJ. Genetics-informed precision treatment formulation in schizophrenia and bipolar disorder. *Am J Hum Genet* 2022; **109**: 1620–1637.
- 20 Zeng B, Bendl J, Kosoy R, Fullard JF, Hoffman GE, Roussos P. Multi-ancestry eQTL meta-analysis of human brain identifies candidate causal variants for brain-related traits. *Nat Genet* 2022; **54**: 161–169.
- 21 Gusev A, Mancuso N, Won H, Kousi M, Finucane HK, Reshef Y *et al.* Transcriptome-wide association study of schizophrenia and chromatin activity yields mechanistic disease insights. *Nat Genet* 2018; **50**: 538–548.
- 22 Rummel CK, Gagliardi M, Ahmad R, Herholt A, Jimenez-Barron L, Murek V *et al.* Massively parallel functional dissection of schizophrenia-associated noncoding genetic variants. *Cell* 2023; **186**: 5165–5182.e33.
- 23 Gandal MJ, Zhang P, Hadjimichael E, Walker RL, Chen C, Liu S *et al.* Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. *Science* 2018; **362**: eaat8127.
- 24 Sey NYA, Hu B, Mah W, Fauni H, McAfee JC, Rajarajan P *et al.* A computational tool (H-MAGMA) for improved prediction of brain-disorder risk genes by incorporating brain chromatin interaction profiles. *Nat Neurosci* 2020; **23**: 583–593.
- 25 Benner C, Spencer CCA, Havulinna AS, Salomaa V, Ripatti S, Pirinen M. FINEMAP: efficient variable selection using summary data from genome-wide association studies. *Bioinformatics* 2016; **32**: 1493–1501.
- 26 Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE *et al.* Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat Genet* 2016; **48**. doi:10.1038/ng.3538.
- 27 Belton JM, McCord RP, Gibcus JH, Naumova N, Zhan Y, Dekker J. Hi-C: a comprehensive technique to capture the conformation of genomes. *Methods* 2012; **58**. doi:10.1016/j.ymeth.2012.05.001.
- 28 Weeks EM, Ulirsch JC, Cheng NY, Trippe BL, Fine RS, Miao J *et al.* Leveraging polygenic

enrichments of gene features to predict genes underlying complex traits and diseases. *Nat Genet* 2023; **55**: 1267–1276.

- 29 de Leeuw CA, Mooij JM, Heskes T, Posthuma D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput Biol* 2015; **11**: e1004219.
- 30 Singh T, Poterba T, Curtis D, Akil H, Al Eissa M, Barchas JD *et al.* Rare coding variants in ten genes confer substantial risk for schizophrenia. *Nature* 2022; **604**: 509–516.
- 31 Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* 2015; **4**: 7.
- 32 Yang J, Ferreira T, Morris AP, Medland SE, Genetic Investigation of ANthropometric Traits (GIANT) Consortium, DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium *et al.* Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat Genet* 2012; **44**: 369–75, S1–3.
- 33 Giambartolomei C, Vukcevic D, Schadt EE, Franke L, Hingorani AD, Wallace C *et al.* Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS Genet* 2014; **10**: e1004383.
- 34 Wallace C. Eliciting priors and relaxing the single causal variant assumption in colocalisation analyses. *PLoS Genet* 2020; **16**: e1008720.
- 35 Frankish A, Diekhans M, Ferreira A-M, Johnson R, Jungreis I, Loveland J *et al.* GENCODE reference annotation for the human and mouse genomes. *Nucleic Acids Res* 2019; **47**: D766–D773.
- 36 Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* 2010; **26**: 2190–2191.
- 37 Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM *et al.* Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. *Nat Genet* 2000; **25**: 25–29.
- 38 Croft D, O'Kelly G, Wu G, Haw R, Gillespie M, Matthews L *et al.* Reactome: a database of reactions, pathways and biological processes. *Nucleic Acids Res* 2011; **39**: D691–7.
- 39 Weissbrod O, Hormozdiari F, Benner C, Cui R, Ulirsch J, Gazal S *et al.* Functionally informed fine-mapping and polygenic localization of complex trait heritability. *Nat Genet* 2020; **52**: 1355–1363.
- 40 Wang QS, Huang H. Methods for statistical fine-mapping and their applications to autoimmune diseases. *Semin Immunopathol* 2022; **44**: 101–113.
- 41 Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T *et al.* Analysis of protein-coding genetic variation in 60,706 humans. *Nature* 2016; **536**: 285–291.
- 42 Satterstrom FK, Kosmicki JA, Wang J, Breen MS, De Rubeis S, An J-Y *et al.* Large-Scale Exome Sequencing Study Implicates Both Developmental and Functional Changes in the Neurobiology of Autism. *Cell* 2020; **180**: 568–584.e23.
- 43 Kaplanis J, Samocha KE, Wiel L, Zhang Z, Arvai KJ, Eberhardt RY *et al.* Evidence for 28

genetic disorders discovered by combining healthcare and research data. *Nature* 2020; **586**: 757–762.

44 Wainberg M, Merico D, Keller MC, Fauman EB, Tripathy SJ. Predicting causal genes from psychiatric genome-wide association studies using high-level etiological knowledge. *Mol Psychiatry* 2022; **27**: 3095–3106.

45 Koscielny G, An P, Carvalho-Silva D, Cham JA, Fumis L, Gasparyan R *et al.* Open Targets: a platform for therapeutic target identification and validation. *Nucleic Acids Res* 2017; **45**: D985–D994.

46 Hatoum AS, Colbert SMC, Johnson EC, Huggett SB, Deak JD, Pathak G *et al.* Multivariate genome-wide association meta-analysis of over 1 million subjects identifies loci underlying multiple substance use disorders. *Nat Ment Health* 2023; **1**: 210–223.

47 Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D *et al.* Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet Neurol* 2019; **18**: 1091–1102.

48 Mealer RG, Williams SE, Noel M, Yang B, D'Souza AK, Nakata T *et al.* The schizophrenia-associated variant in SLC39A8 alters protein glycosylation in the mouse brain. *Mol Psychiatry* 2022; **27**: 1405–1415.

49 Hatzimanolis A, Foteli S, Stefanatou P, Ntigrintaki A-A, Ralli I, Kollias K *et al.* Dereulation of complement components C4A and CSMD1 peripheral expression in first-episode psychosis and links to cognitive ability. *Eur Arch Psychiatry Clin Neurosci* 2022; **272**: 1219–1228.

50 Steen VM, Nepal C, Ersland KM, Holdhus R, Nævdal M, Ratvik SM *et al.* Neuropsychological deficits in mice depleted of the schizophrenia susceptibility gene CSMD1. *PLoS One* 2013; **8**: e79501.

51 Wang S, Che T, Levit A, Shoichet BK, Wacker D, Roth BL. Structure of the D2 dopamine receptor bound to the atypical antipsychotic drug risperidone. *Nature* 2018; **555**: 269–273.

52 Borcuk C, Parihar M, Sportelli L, Kleinman JE, Shin JH, Hyde TM *et al.* Network-wide risk convergence in gene co-expression identifies reproducible genetic hubs of schizophrenia risk. *Neuron* 2024; **112**: 3551–3566.e6.

53 Pergola G, Parihar M, Sportelli L, Bharadwaj R, Borcuk C, Radulescu E *et al.* Consensus molecular environment of schizophrenia risk genes in coexpression networks shifting across age and brain regions. *Sci Adv* 2023; **9**: eade2812.

54 Bhattacharya A, Vo DD, Jops C, Kim M, Wen C, Hervoso JL *et al.* Isoform-level transcriptome-wide association uncovers genetic risk mechanisms for neuropsychiatric disorders in the human brain. *Nat Genet* 2023; **55**: 2117–2128.

55 Deans PJM, Townsley KG, Li A, Seah C, Johnson J, Gonzalez JG *et al.* Convergent and non-additive impact of schizophrenia risk genes in human neurons. *bioRxiv*. 2022; : 2022.03.29.486286.

56 McAfee JC, Lee S, Lee J, Bell JL, Krupa O, Davis J *et al.* Systematic investigation of allelic

regulatory activity of schizophrenia-associated common variants. *Cell Genom* 2023; **3**: 100404.

57 Rajarajan P, Borrman T, Liao W, Schrode N, Flaherty E, Casiño C *et al.* Neuron-specific signatures in the chromosomal connectome associated with schizophrenia risk. *Science* 2018; **362**. doi:10.1126/science.aat4311.

58 Finan C, Gaulton A, Kruger FA, Lumbers RT, Shah T, Engmann J *et al.* The druggable genome and support for target identification and validation in drug development. *Sci Transl Med* 2017; **9**. doi:10.1126/scitranslmed.aag1166.

59 Wang Q, Chen R, Cheng F, Wei Q, Ji Y, Yang H *et al.* A Bayesian framework that integrates multi-omics data and gene networks predicts risk genes from schizophrenia GWAS data. *Nat Neurosci* 2019; **22**: 691–699.

60 Lago SG, Bahn S. The druggable schizophrenia genome: from repurposing opportunities to unexplored drug targets. *NPJ Genom Med* 2022; **7**: 25.

61 Karunakaran KB, Chaparala S, Ganapathiraju MK. Potentially repurposable drugs for schizophrenia identified from its interactome. *Sci Rep* 2019; **9**: 12682.

62 Farsi Z, Nicolella A, Simmons SK, Aryal S, Shepard N, Brenner K *et al.* Brain-region-specific changes in neurons and glia and dysregulation of dopamine signaling in Grin2a mutant mice. *Neuron* 2023; **111**: 3378–3396.e9.

63 Wasserthal S, Lehmann M, Neumann C, Delis A, Philipsen A, Hurlemann R *et al.* Effects of NMDA-receptor blockade by ketamine on mentalizing and its neural correlates in humans: a randomized control trial. *Sci Rep* 2023; **13**: 17184.

64 Goh KK, Wu T-H, Chen C-H, Lu M-L. Efficacy of -methyl--aspartate receptor modulator augmentation in schizophrenia: A meta-analysis of randomised, placebo-controlled trials. *J Psychopharmacol* 2021; **35**: 236–252.

65 de Bartolomeis A, Vellucci L, Austin MC, De Simone G, Barone A. Rational and Translational Implications of D-Amino Acids for Treatment-Resistant Schizophrenia: From Neurobiology to the Clinics. *Biomolecules* 2022; **12**. doi:10.3390/biom12070909.

66 Rosenbrock H, Desch M, Wunderlich G. Development of the novel GlyT1 inhibitor, icleperitin (BI 425809), for the treatment of cognitive impairment associated with schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2023; **273**: 1557–1566.

67 Dogra S, Putnam J, Conn PJ. Metabotropic glutamate receptor 3 as a potential therapeutic target for psychiatric and neurological disorders. *Pharmacol Biochem Behav* 2022; **221**: 173493.

68 Downing AM, Kinon BJ, Millen BA, Zhang L, Liu L, Morozova MA *et al.* A Double-Blind, Placebo-Controlled Comparator Study of LY2140023 monohydrate in patients with schizophrenia. *BMC Psychiatry* 2014; **14**: 351.

69 Adams DH, Zhang L, Millen BA, Kinon BJ, Gomez J-C. Pomaglumetad Methionil (LY2140023 Monohydrate) and Aripiprazole in Patients with Schizophrenia: A Phase 3, Multicenter, Double-Blind Comparison. *Schizophr Res Treatment* 2014; **2014**: 758212.

70 Kinon BJ, Zhang L, Millen BA, Osuntokun OO, Williams JE, Kollack-Walker S *et al.* A multicenter, inpatient, phase 2, double-blind, placebo-controlled dose-ranging study of LY2140023 monohydrate in patients with DSM-IV schizophrenia. *J Clin Psychopharmacol* 2011; **31**: 349–355.

71 Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV *et al.* Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. *Nat Med* 2007; **13**: 1102–1107.

72 Kinon BJ, Millen BA, Zhang L, McKinzie DL. Exploratory analysis for a targeted patient population responsive to the metabotropic glutamate 2/3 receptor agonist pomaglumetad methionil in schizophrenia. *Biol Psychiatry* 2015; **78**. doi:10.1016/j.biopsych.2015.03.016.

73 Dogra S, Stansley BJ, Xiang Z, Qian W, Gogliotti RG, Nicoletti F *et al.* Activating mGlu Metabotropic Glutamate Receptors Rescues Schizophrenia-like Cognitive Deficits Through Metaplastic Adaptations Within the Hippocampus. *Biol Psychiatry* 2021; **90**: 385–398.

74 Jin LE, Wang M, Galvin VC, Lightbourne TC, Conn PJ, Arnsten AFT *et al.* mGluR2 versus mGluR3 Metabotropic Glutamate Receptors in Primate Dorsolateral Prefrontal Cortex: Postsynaptic mGluR3 Strengthen Working Memory Networks. *Cereb Cortex* 2018; **28**: 974–987.

75 Maksymetz J, Byun NE, Luessen DJ, Li B, Barry RL, Gore JC *et al.* mGlu potentiation enhances prelimbic somatostatin interneuron activity to rescue schizophrenia-like physiological and cognitive deficits. *Cell Rep* 2021; **37**: 109950.

76 Stansley BJ, Conn PJ. The therapeutic potential of metabotropic glutamate receptor modulation for schizophrenia. *Curr Opin Pharmacol* 2018; **38**: 31–36.

77 Yohn SE, Foster DJ, Covey DP, Moehle MS, Galbraith J, Garcia-Barrantes PM *et al.* Activation of the mGlu metabotropic glutamate receptor has antipsychotic-like effects and is required for efficacy of M muscarinic receptor allosteric modulators. *Mol Psychiatry* 2020; **25**: 2786–2799.

78 Paul SM, Yohn SE, Brannan SK, Neugebauer NM, Breier A. Muscarinic Receptor Activators as Novel Treatments for Schizophrenia. *Biol Psychiatry* 2024; **96**: 627–637.

79 Mallinger AG, Thase ME, Haskett R, Buttenfield J, Luckenbaugh DA, Frank E *et al.* Verapamil augmentation of lithium treatment improves outcome in mania unresponsive to lithium alone: preliminary findings and a discussion of therapeutic mechanisms. *Bipolar Disord* 2008; **10**: 856–866.

80 Mullins N, Forstner AJ, O'Connell KS, Coombes B, Coleman JRI, Qiao Z *et al.* Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat Genet* 2021; **53**: 817–829.

81 Lintunen J, Lähteenluoma M, Tiihonen J, Tanskanen A, Taipale H. Adenosine modulators and calcium channel blockers as add-on treatment for schizophrenia. *NPJ Schizophr* 2021; **7**: 1.

82 Vahdani B, Armani KA, Esmaeilzadeh A, Zenoozian S, Yousefi V, Mazloomzadeh S. Adjunctive Raloxifene and Isradipine Improve Cognitive Functioning in Patients With Schizophrenia: A Pilot Study. *J Clin Psychopharmacol* 2020; **40**.

doi:10.1097/JCP.0000000000001274.

- 83 Zink CF, Giegerich M, Prettyman GE, Carta KE, van Ginkel M, O'Rourke MP *et al.* Nimodipine improves cortical efficiency during working memory in healthy subjects. *Transl Psychiatry* 2020; **10**: 372.
- 84 Egan MF, Zhao X, Smith A, Troyer MD, Uebele VN, Pidkortov V *et al.* Randomized controlled study of the T-type calcium channel antagonist MK-8998 for the treatment of acute psychosis in patients with schizophrenia. *Hum Psychopharmacol* 2013; **28**: 124–133.
- 85 Greco LA, Reay WR, Dayas CV, Cairns MJ. Pairwise genetic meta-analyses between schizophrenia and substance dependence phenotypes reveals novel association signals with pharmacological significance. *Transl Psychiatry* 2022; **12**: 403.
- 86 Spanagel R. Animal models of addiction. *Dialogues Clin Neurosci* 2017; **19**: 247–258.
- 87 Antonelli M, Sestito L, Tarli C, Addolorato G. Perspectives on the pharmacological management of alcohol use disorder: Are the approved medications effective? *Eur J Intern Med* 2022; **103**: 13–22.
- 88 Bell RL, Lopez MF, Cui C, Egli M, Johnson KW, Franklin KM *et al.* Ibudilast reduces alcohol drinking in multiple animal models of alcohol dependence. *Addict Biol* 2015; **20**: 38–42.
- 89 Grodin EN, Bujarski S, Towns B, Burnette E, Nieto S, Lim A *et al.* Ibudilast, a neuroimmune modulator, reduces heavy drinking and alcohol cue-elicited neural activation: a randomized trial. *Transl Psychiatry* 2021; **11**: 355.
- 90 Gilleen J, Farah Y, Davison C, Kerins S, Valdearenas L, Uz T *et al.* An experimental medicine study of the phosphodiesterase-4 inhibitor, roflumilast, on working memory-related brain activity and episodic memory in schizophrenia patients. *Psychopharmacology* 2021; **238**: 1279–1289.
- 91 Tesli M, Wirgenes KV, Hughes T, Bettella F, Athanasiu L, Hoseth ES *et al.* VRK2 gene expression in schizophrenia, bipolar disorder and healthy controls. *Br J Psychiatry* 2016; **209**: 114–120.
- 92 Lee J, Lee S, Ryu Y-J, Lee D, Kim S, Seo J-Y *et al.* Vaccinia-related kinase 2 plays a critical role in microglia-mediated synapse elimination during neurodevelopment. *Glia* 2019; **67**: 1667–1679.
- 93 Ochoa D, Hercules A, Carmona M, Suveges D, Baker J, Malangone C *et al.* The next-generation Open Targets Platform: reimagined, redesigned, rebuilt. *Nucleic Acids Res* 2023; **51**: D1353–D1359.
- 94 Parellada M, San José Cáceres A, Palmer M, Delorme R, Jones EJH, Parr JR *et al.* A Phase II randomized, double-blind, placebo-controlled Study of the efficacy, safety, and tolerability of arbaclofen administered for the treatment of social function in children and adolescents with autism spectrum disorders: Study protocol for AIMS-2-TRIALS-CT1. *Front Psychiatry* 2021; **12**: 701729.
- 95 Grent-t-Jong T, Gross J, Goense J, Wibral M, Gajwani R, Gumley AI *et al.* Resting-state gamma-band power alterations in schizophrenia reveal E/I-balance abnormalities across

illness-stages. *Elife* 2018; **7**. doi:10.7554/eLife.37799.

96 Fatemi SH, Folsom TD, Thuras PD. Deficits in GABA(B) receptor system in schizophrenia and mood disorders: a postmortem study. *Schizophr Res* 2011; **128**: 37–43.

97 Orhan F, Fatouros-Bergman H, Goiny M, Malmqvist A, Piehl F, Karolinska Schizophrenia Project (KaSP) Consortium *et al.* CSF GABA is reduced in first-episode psychosis and associates to symptom severity. *Mol Psychiatry* 2018; **23**: 1244–1250.

98 Rowland LM, Kontson K, West J, Edden RA, Zhu H, Wijtenburg SA *et al.* In vivo measurements of glutamate, GABA, and NAAG in schizophrenia. *Schizophr Bull* 2013; **39**: 1096–1104.

99 Chiu PW, Lui SSY, Hung KSY, Chan RCK, Chan Q, Sham PC *et al.* In vivo gamma-aminobutyric acid and glutamate levels in people with first-episode schizophrenia: A proton magnetic resonance spectroscopy study. *Schizophr Res* 2018; **193**: 295–303.

100 De Crescenzo F, Postorino V, Siracusano M, Riccioni A, Armando M, Curatolo P *et al.* Autistic Symptoms in Schizophrenia Spectrum Disorders: A Systematic Review and Meta-Analysis. *Front Psychiatry* 2019; **10**: 78.

101 Oliver LD, Moxon-Emre I, Lai MC, Grennan L, Voineskos AN, Ameis SH. Social Cognitive Performance in Schizophrenia Spectrum Disorders Compared With Autism Spectrum Disorder: A Systematic Review, Meta-analysis, and Meta-regression. *JAMA Psychiatry* 2021; **78**. doi:10.1001/jamapsychiatry.2020.3908.

102 Mullard A. FDA approves first-in-class AKT inhibitor. *Nat Rev Drug Discov* 2024; **23**: 9.

103 Tsimberidou A-M, Skliris A, Valentine A, Shaw J, Hering U, Vo HH *et al.* AKT inhibition in the central nervous system induces signaling defects resulting in psychiatric symptomatology. *Cell Biosci* 2022; **12**: 56.

104 Bergeron Y, Bureau G, Laurier-Laurin M-É, Asselin E, Massicotte G, Cyr M. Genetic Deletion of Akt3 Induces an Endophenotype Reminiscent of Psychiatric Manifestations in Mice. *Front Mol Neurosci* 2017; **10**: 102.

105 Howell KR, Floyd K, Law AJ. PKB γ /AKT3 loss-of-function causes learning and memory deficits and deregulation of AKT/mTORC2 signaling: Relevance for schizophrenia. *PLoS One* 2017; **12**: e0175993.

106 Lang AE, Siderowf AD, Macklin EA, Poewe W, Brooks DJ, Fernandez HH *et al.* Trial of Cinpanemab in Early Parkinson's Disease. *N Engl J Med* 2022; **387**: 408–420.

107 Pagano G, Taylor KI, Anzures-Cabrera J, Marchesi M, Simuni T, Marek K *et al.* Trial of Prasinezumab in Early-Stage Parkinson's Disease. *N Engl J Med* 2022; **387**: 421–432.

108 Soldner F, Stelzer Y, Shivalila CS, Abraham BJ, Latourelle JC, Barrasa MI *et al.* Parkinson-associated risk variant in distal enhancer of α -synuclein modulates target gene expression. *Nature* 2016; **533**: 95–99.

109 Mostafavi H, Spence JP, Naqvi S, Pritchard JK. Systematic differences in discovery of genetic effects on gene expression and complex traits. *Nat Genet* 2023; **55**: 1866–1875.

110 Kanai M, Elzur R, Zhou W, Global Biobank Meta-analysis Initiative, Daly MJ, Finucane HK. Meta-analysis fine-mapping is often miscalibrated at single-variant resolution. *Cell Genom* 2022; **2**. doi:10.1016/j.xgen.2022.100210.

ARTICLE IN PRESS

Figure legends

Figure 1. Heatmap

An overview of the evidence supporting each prioritized gene, separated based on whether they were (left panel) or were not (middle and continued in the right panel) previously prioritized in the PGC3 study¹⁷. Distance: distance in kilobases between gene and credible set. PoPS: PoPS percentile where 0 represents the smallest genome-wide value and 1 represents the largest. # genes: number of genes in the locus. SCHEMA: a binary indicator of whether ultra-rare coding variant burden in a given gene was also significantly associated ($P_{FDR} < 5\%$) with schizophrenia in a study from the Schizophrenia Exome Sequencing Meta-analysis (SCHEMA) consortium³⁰. Non-synonymous: a binary indicator of whether the credible set contained non-synonymous variants with a summed posterior inclusion probability $>50\%$. Genes are sorted first by “Non-synonymous”, then by SCHEMA, distance, and PoPS percentile.

Figure 2. Venn diagram

Venn diagram showing the overlap between the number of genes identified by the present analysis (PoPS⁺), rare-variant studies of autism spectrum disorder (ASD) and/or developmental disorder (DD), the Psychiatric Omnilocus Prioritization Score (PsyOPS), and prior gene prioritization efforts (PGC3). Gene symbols are displayed for a subset of intersecting regions.

Figure 3. Variant-level associations and PoPS results for selected loci

The prioritized genes in plots **A-E** are targets of approved drugs; the prioritized genes in plots **E-F** are in loci shared by an addiction GWAS⁴⁶. The upper portion of each sub-plot is a LocusZoom plot. Each point represents a different genetic variant, the x-axis represents physical position on the listed chromosome, the left y-axis represents $-\log_{10}$ -transformed P value, the right y-axis represents the recombination rate, colour represents linkage disequilibrium with the lead variant in the locus (as shown in the legend), and the horizontal dashed line represents the genome-wide significance P value threshold of 5×10^{-8} . The lower portion of each figure is a PoPS

plot. Genes are denoted as blue bars spanning from their transcription start site to their transcription stop site using the same x-axis as the LocusZoom plot, the y-axis represents the raw PoPS score, the dashed horizontal grey lines represent the top 10% and 1% of PoPS scores genome-wide, and the solid horizontal grey line represents a PoPS score of 0.

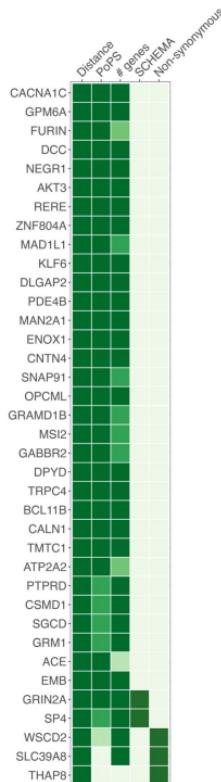
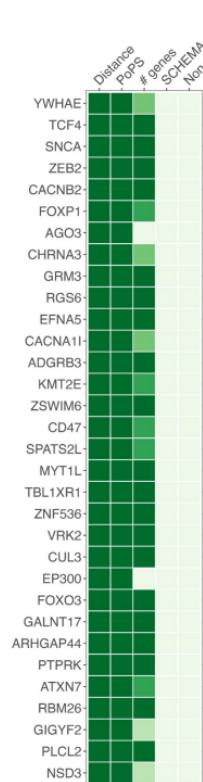
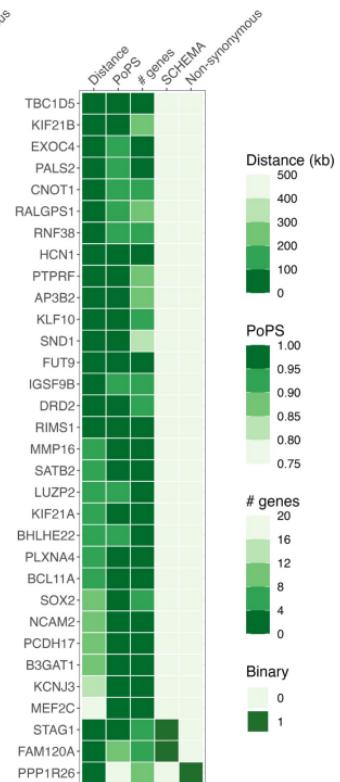
ARTICLE IN PRESS

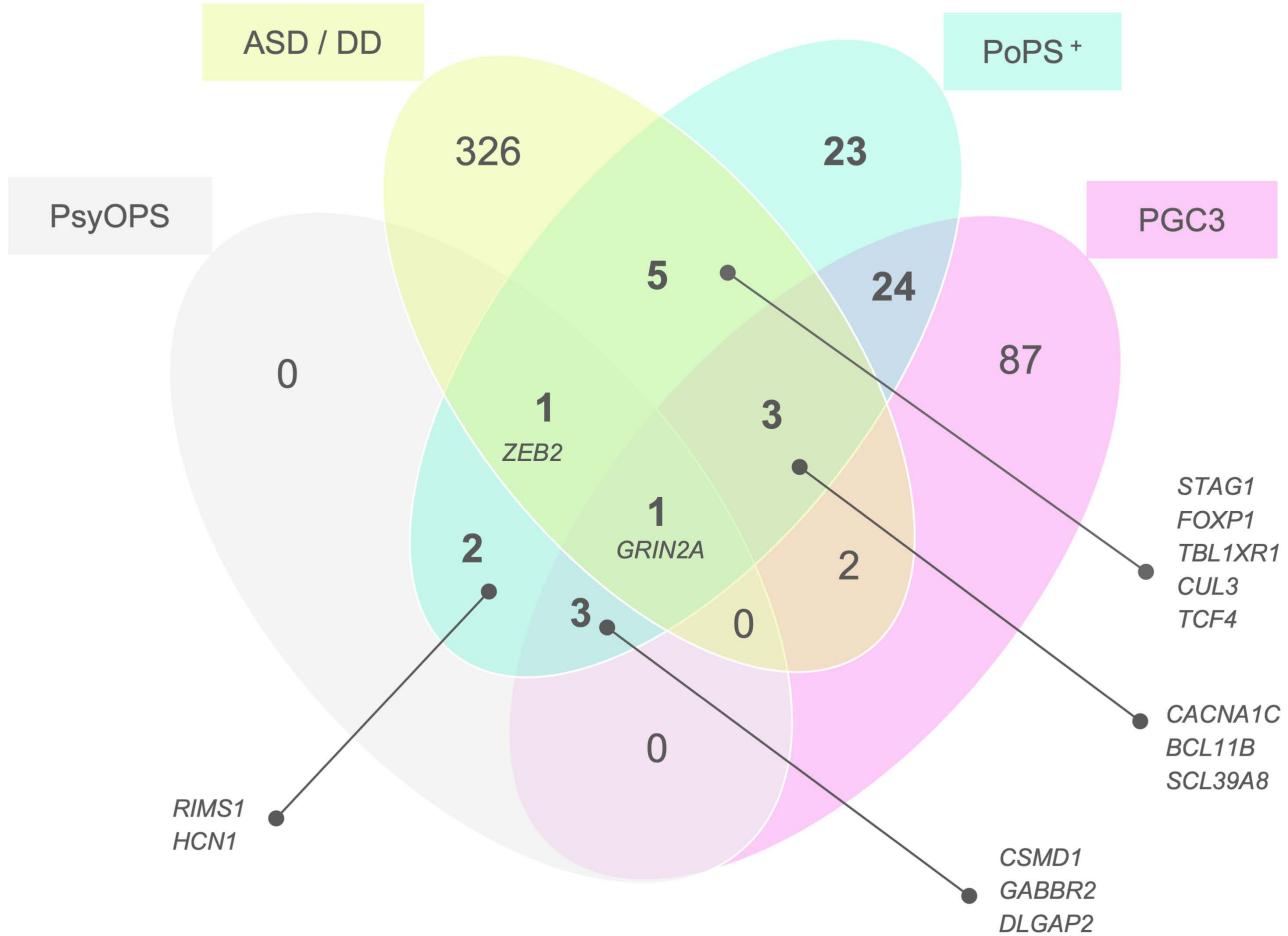
Tables

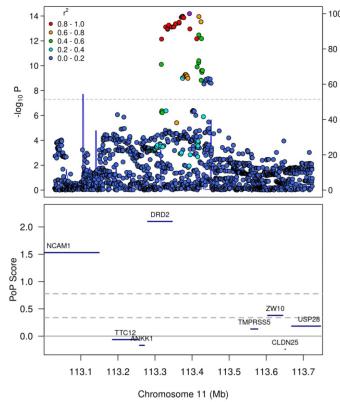
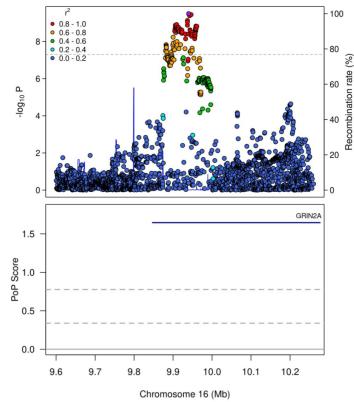
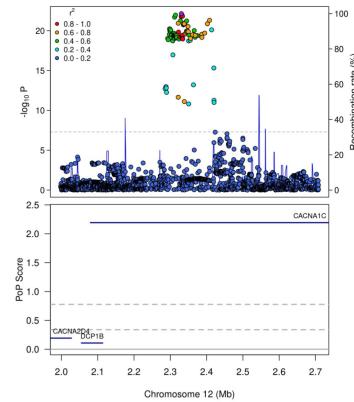
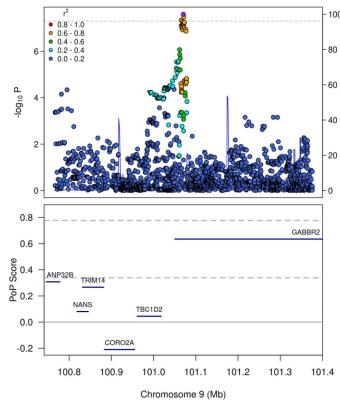
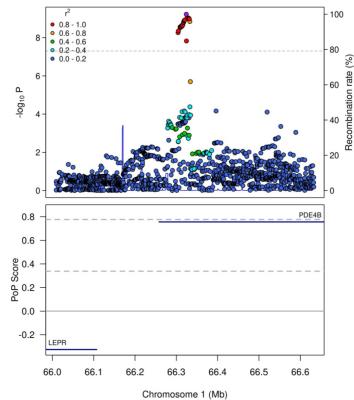
Table 1. Prioritized genes targeted by approved or investigational drugs, or nominated by tractability analysis

Level of evidence	Genes
Clinical trial, schizophrenia	<i>DRD2</i> ^A , <i>GRIN2A</i> ^A , <i>CACNA1C</i> ^A , <i>GRM3</i> , <i>CACNA10</i> ^A , <i>PDE4B</i> ^A
Clinical trial, other psychiatric disease	<i>GABBR2</i> ^A , <i>CHRNA3</i> ^A , <i>CACNB2</i> ^A , <i>ACE</i> ^A
Clinical trial, non-psychiatric disease	<i>CD47</i> , <i>ATP2A2</i> , <i>KCNJ3</i> ^A , <i>AKT3</i> ^A , <i>DPYD</i> , <i>SNCA</i>
Predicted to be tractable	<i>HCN1</i> , <i>VRK2</i> , <i>TRPC4</i> , <i>EP300</i> , <i>GRM1</i> , <i>PTPRF</i> , <i>MMP16</i>

^A – targeted by approved drugs

Genes also prioritized by PGC3**Genes not prioritized by PGC3****Genes not prioritized by PGC3 (continued)**



A. DRD2**B. GRIN2A****C. CACNA1C****D. GABBR2****E. PDE4B****F. VRK2**